

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Article 36 and Rule 70)

REC'D 01 APR 2005

WIPO

PCT

Applicant's or agent's file reference <b>4-32778AUSN</b>	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. <b>PCT/EP 03/13963</b>	International filing date ( <i>day/month/year</i> ) <b>09.12.2003</b>	Priority date ( <i>day/month/year</i> ) <b>10.12.2002</b>
International Patent Classification (IPC) or both national classification and IPC <b>A61K31/40</b>		
Applicant <b>NOVARTIS AG</b>		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
 

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:
 

I ☒ Basis of the opinion

II ☐ Priority

III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

IV ☐ Lack of unity of invention

V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

VI ☐ Certain documents cited

VII ☐ Certain defects in the international application

VIII ☐ Certain observations on the international application

Date of submission of the demand  <b>07.05.2004</b>	Date of completion of this report  <b>04.04.2005</b>
Name and mailing address of the international preliminary examining authority:  <div style="display: flex; align-items: center;"> <div>             European Patent Office - P.B. 5818 Patentlaan 2              NL-2280 HV Rijswijk - Pays Bas              Tel. +31 70 340 - 2040 Tx: 31 651 epo nl              Fax: +31 70 340 - 3016           </div> </div>	Authorized Officer  <b>Leherte, C</b>  Telephone No. +31 70 340-2748



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/13963

## I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):*

### Description, Pages

1-27 as originally filed

### Claims, Numbers

1-20 received on 23.02.2005 with letter of 18.02.2005

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

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**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1, 2, 4-19

because:

☒ the said international application, or the said claims Nos. 9-11 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1, 2, 4-19 (all partially)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	1, 2, 4-7, 9-13, 15-19
Inventive step (IS)	Yes: Claims	
	No: Claims	1-20
Industrial applicability (IA)	Yes: Claims	
	No: Claims	see separate sheet

2. Citations and explanations

**see separate sheet**

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

**1) LACK OF CLARITY, SUPPORT AND DISCLOSURE**

1.1. Claims 1, 2, 4-7, 9-13 and 15-19 encompass a genus of compounds defined only by their function ("peroxisome proliferator-activated receptor alpha compound"), wherein the relationship between the structural features of the members of the genus and said function have not been defined. In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition.

The fact that one could have assayed a compound of interest using the claimed assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity.

The claims cover all combinations of dipeptidylpeptidase IV inhibitors of formula I and peroxisome proliferator-activated receptor alpha compounds, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a limited amount of such combinations.

1.2. Present claims 6-9, 12-16 and 18 relate to an extremely large number of disease states. In fact, the expressions "conditions mediated by DPP-IV or PPAR alpha", "conditions of IGT" and "conditions of impaired fasting plasma glucose" encompass a great number of diseases. A lack of clarity (and/or conciseness) within the meaning of Art. 6 PCT therefore arises.

Independent of the above, the Applicant has not provided any test to demonstrate whether a disease is associated with conditions mediated by DPP-IV or PPAR alpha, conditions of IGT or conditions of impaired fasting plasma glucose or not. There is therefore insufficient disclosure (Art. 5 PCT) to allow the skilled man to determine which diseases fall within the definition.

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1.3. The attention of the applicant is drawn to the fact that for the present application only an incomplete search has been carried out (see sheet PCT/ISA/210, and in particular the last paragraph). The examination will be carried out accordingly.

**2) METHOD OF TREATMENT**

Claims 9-11 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

The present opinion expressed as to novelty, inventive step and industrial applicability refers only to matter for which an international search report has been drawn up (i.e. the use of the combinations specifically mentioned in claims 8, 14 and 22 for the treatment of diseases explicitly mentioned in claims 10, 11 and 17.

**1) INDUSTRIAL APPLICABILITY**

Claims 9-11 involve compositions or substances in a method of treatment of the human/animal body. For the assessment of such claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**2) DOCUMENTS USED IN EXAMINATION**

Reference is made to the following documents:

D1: WO-A-02083128

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D2: WO-A-0152825 (cited in the application)

D3: WO-A-02064094

D4: WO-A-0160807

Unless indicated otherwise reference is made to the passages considered relevant in the search report.

**3) AMENDMENTS**

The amendments of the claims filed with the letter of 18.02.2005 are permissible under article 34(2)(b) PCT, since they do not introduce subject-matter which extends beyond the content of the application as originally filed.

**4) NOVELTY**

The present application does not meet the requirements of Article 33 (2) PCT, because the subject-matter of claims 1, 2, 4-7, 9-13 and 15-19 is not new in the sense of Article 33 (3) PCT.

Document D2 already discloses the use of pharmaceutical combinations containing dipeptidylpeptidase IV inhibitors of formula I( DPP728, LAF237) with peroxisome proliferator-activated receptor alpha compounds for the treatment of type 2 diabetes, impaired glucose tolerance, metabolic acidosis, ketosis, arthritis, obesity and osteoporosis. Thus, it is prejudicial to the novelty of the subject-matter of claims 1, 2, 4-7, 9-13 and 15-19.

**5) INVENTIVE STEP**

The present application does not meet the requirements of Article 33(3) PCT, because the subject-matter of claims 1-20 does not involve an inventive step.

The problem to be solved by the present application is the provision of an alternative medicament for treating dyslipidemia, diabetes, type 2 diabetes, obesity, impaired glucose tolerance, metabolic acidosis, ketosis, arthritis and osteoporosis.

The solution proposed by the applicant is a combination of a dipeptidylpeptidase IV

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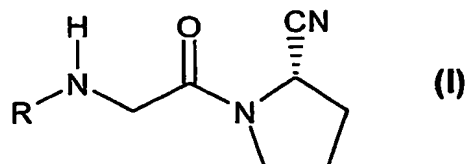
inhibitor of formula I with a peroxisome proliferator-activated receptor alpha compound. Document D1, D2, D3 and D4 which are considered to represent the most relevant state of the art, disclose methods of treatment of dyslipidemia, diabetes, type 2 diabetes, obesity, impaired glucose tolerance, metabolic acidosis, ketosis, arthritis and osteoporosis with combinations of a dipeptidylpeptidase IV inhibitors and peroxisome proliferator-activated receptor compounds.

The subject-matter of the claims differs in that other dipeptidylpeptidase IV inhibitors and/or other peroxisome proliferator-activated receptor compounds are used in the combinations.

The use of a combination of two or more active ingredients with known identical therapeutic use can only be considered as inventive when a surprising effect, an unexpected high synergistic effect or reduced side effects for example, can be assigned in relation to the claimed therapeutic use. In this respect, the present application lacks supportive evidence.

**WHAT IS CLAIMED IS:**

1. Combination comprising a dipeptidylpeptidase-IV (DPP-IV) inhibitor which is a *N*-(*N'*-substituted glycyI)-2-cyanopyrrolidine of formula (I)



wherein R is:

- a)  $R_1R_{1a}N(CH_2)_m$ ,

wherein

$R_1$  is a pyridinyl or pyrimidinyl moiety optionally mono- or, independently, di-substituted with lower alkyl, lower alkoxy, halogen, trifluoromethyl, cyano or nitro; or phenyl optionally mono- or, independently, di-substituted with lower alkyl, lower alkoxy or halogen;

$R_{1a}$  is hydrogen or  $(C_{1-8})$ alkyl; and

$m$  is 2 or 3;

- b)  $(C_{3-12})$ Cycloalkyl optionally mono-substituted in the 1-position with  $(C_{1-3})$ hydroxyalkyl;

- c)  $R_2(CH_2)_n$ ,

wherein either

$R_2$  is phenyl optionally mono- or independently di- or, independently, tri-substituted with lower alkyl, lower alkoxy, halogen or phenylthio optionally mono-substituted in the phenyl ring with hydroxymethyl; or is  $(C_{1-8})$ alkyl; a [3.1.1]bicyclic carbocyclic moiety optionally mono- or pluri-substituted with  $(C_{1-8})$ alkyl; a pyridinyl or naphthyl moiety optionally mono- or, independently, di-substituted with lower alkyl, lower alkoxy or halogen; cyclohexene; or adamantyl; and

$n$  is 1-3; or

$R_2$  is phenoxy optionally mono- or, independently, di-substituted with lower alkyl, lower alkoxy or halogen; and

$n$  is 2 or 3;

- d)  $(R_3)_2CH(CH_2)_2$ , wherein each  $R_3$ , independently, is phenyl optionally mono- or, independently, di-substituted with lower alkyl, lower alkoxy or halogen;

- e)  $R_4(CH_2)_p$ ,



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wherein

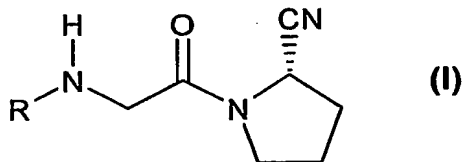
$R_4$  is 2-oxopyrrolidinyl or  $(C_{2-4})$ alkoxy; and

$p$  is 2-4;

- f) isopropyl optionally mono-substituted in 1-position with  $(C_{1-3})$ hydroxyalkyl;
- g)  $R_5$ , wherein  $R_5$  is indanyl, a pyrrolidinyl or piperidinyl moiety optionally substituted with benzyl, a [2.2.1]- or [3.1.1]bicyclic carbocyclic moiety optionally mono- or pluri-substituted with  $(C_{1-8})$ alkyl, adamantyl or  $(C_{1-8})$ alkyl optionally mono- or, independently, pluri-substituted with hydroxy, hydroxymethyl or phenyl optionally mono- or, independently, di-substituted with lower alkyl, lower alkoxy or halogen;
- h) a substituted adamantyl
- in free form or in acid addition salt form;

and at least one peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ ) in free form or in acid addition salt form.

2. A pharmaceutical composition comprising a DPP-IV inhibitor which is a  $N$ -( $N'$ -substituted glycol)-2-cyanopyrrolidine of formula (I)



wherein  $R$  is:

- a)  $R_1R_{1a}N(CH_2)_m$ ,

wherein

$R_1$  is a pyridinyl or pyrimidinyl moiety optionally mono- or, independently, di-substituted with lower alkyl, lower alkoxy, halogen, trifluoromethyl, cyano or nitro; or phenyl optionally mono- or, independently, di-substituted with lower alkyl, lower alkoxy or halogen;

$R_{1a}$  is hydrogen or  $(C_{1-8})$ alkyl; and

$m$  is 2 or 3;

- b)  $(C_{3-12})$ Cycloalkyl optionally mono-substituted in the 1-position with  $(C_{1-3})$ hydroxyalkyl;

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c)  $R_2(CH_2)_n-$ ,

wherein either

$R_2$  is phenyl optionally mono- or independently di- or, independently, tri-substituted with lower alkyl, lower alkoxy, halogen or phenylthio optionally mono-substituted in the phenyl ring with hydroxymethyl; or is  $(C_{1-8})$ alkyl; a [3.1.1]bicyclic carbocyclic moiety optionally mono- or pluri-substituted with  $(C_{1-8})$ alkyl; a pyridinyl or naphthyl moiety optionally mono- or, independently, di-substituted with lower alkyl, lower alkoxy or halogen; cyclohexene; or adamantyl; and

 $n$  is 1-3; or

$R_2$  is phenoxy optionally mono- or, independently, di-substituted with lower alkyl, lower alkoxy or halogen; and

 $n$  is 2 or 3;d)  $(R_3)_2CH(CH_2)_2-$ , wherein each  $R_3$ , independently, is phenyl optionally mono- or, independently, di-substituted with lower alkyl, lower alkoxy or halogen;e)  $R_4(CH_2)_p-$ ,

wherein

 $R_4$  is 2-oxopyrrolidinyl or  $(C_{2-4})$ alkoxy; and $p$  is 2-4;f) isopropyl optionally mono-substituted in 1-position with  $(C_{1-3})$ hydroxyalkyl;g)  $R_5$ , wherein  $R_5$  is indanyl, a pyrrolidinyl or piperidinyl moiety optionally substituted with benzyl, a [2.2.1]- or [3.1.1]bicyclic carbocyclic moiety optionally mono- or pluri-substituted with  $(C_{1-8})$ alkyl, adamantyl or  $(C_{1-8})$ alkyl optionally mono- or, independently, pluri-substituted with hydroxy, hydroxymethyl or phenyl optionally mono- or, independently, di-substituted with lower alkyl, lower alkoxy or halogen;

h) a substituted adamantyl

in free form or in acid addition salt form;

and at least one further  $PPAR\alpha$  compound or the pharmaceutically acceptable salt of such a compound and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use.

3. The pharmaceutical composition according to claim 1, wherein the further  $PPAR\alpha$  compound is selected from the group consisting of fenofibrate, micronized fenofibrate,

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bezafibrate, gemfibrazil and ciprofibrate or the pharmaceutically acceptable salt of such a compound.

4. The pharmaceutical composition according to claim 1, which is a fixed combination.

5. The pharmaceutical composition according to claim 1, which is a combined preparation.

6. The pharmaceutical composition according to claim 5 which is a combined preparation for simultaneous, separate or sequential use in the prevention, delay of progression or treatment of conditions mediated by DPP-IV or PPAR $\alpha$ .

7. The combination according to claim 1 or a pharmaceutical composition according to any one of claims 2 to 6, wherein the DPP-IV inhibitor a compound of formula (I) which is selected from

(S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine; and

(S)-1-{2-[5-cyanopyridin-2-yl)amino]ethyl-aminoacetyl}-2-cyano-pyrrolidine;

in free form or in acid addition salt form.

8. The combination according to claim 1 or a pharmaceutical composition according to any one of claims 2 to 6, wherein the DPP-IV inhibitor is selected from

(S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine; and

(S)-1-{2-[5-cyanopyridin-2-yl)amino]ethyl-aminoacetyl}-2-cyano-pyrrolidine,

and the further PPAR $\alpha$  compound is selected from the group consisting of fenofibrate, micronized fenofibrate, bezafibrate, gemfibrazil and ciprofibrate,

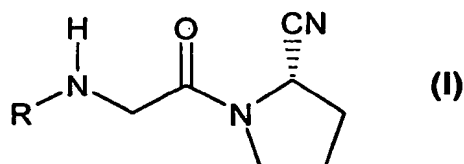
or the pharmaceutically acceptable salt of such a compound.

9. A method of treating a condition mediated by DPP-IV or PPAR $\alpha$  comprising administering to a warm-blooded animal in need thereof jointly therapeutically effective amounts of a DPP-IV inhibitor as defined in claim 1, in free or pharmaceutically acceptable salt form and at least one PPAR $\alpha$  compound, or the pharmaceutically acceptable salts of such compounds.

10. The method of claim 9, wherein the condition is dyslipidemia or obesity.

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11. The method of claim 9, wherein the condition is diabetes preferably type II diabetes.
12. A combination or pharmaceutical composition according to any one of the claims 1 to 8, for use as a medicament.
13. Use of a DPP-IV inhibitor which is a *N*-(*N'*-substituted glycyI)-2-cyanopyrrolidine of formula (I)



wherein R is:

- a)  $R_1R_{1a}N(CH_2)_m$ ,

wherein

$R_1$  is a pyridinyl or pyrimidinyl moiety optionally mono- or, independently, di-substituted with lower alkyl, lower alkoxy, halogen, trifluoromethyl, cyano or nitro; or phenyl optionally mono- or, independently, di-substituted with lower alkyl, lower alkoxy or halogen;

$R_{1a}$  is hydrogen or  $(C_{1-8})$ alkyl; and

$m$  is 2 or 3;

- b)  $(C_{3-12})$ Cycloalkyl optionally mono-substituted in the 1-position with  $(C_{1-3})$ hydroxyalkyl;

- c)  $R_2(CH_2)_n$ ,

wherein either

$R_2$  is phenyl optionally mono- or independently di- or, independently, tri-substituted with lower alkyl, lower alkoxy, halogen or phenylthio optionally mono-substituted in the phenyl ring with hydroxymethyl; or is  $(C_{1-8})$ alkyl; a [3.1.1]bicyclic carbocyclic moiety optionally mono- or pluri-substituted with  $(C_{1-8})$ alkyl; a pyridinyl or naphthyl moiety optionally mono- or, independently, di-substituted with lower alkyl, lower alkoxy or halogen; cyclohexene; or adamantyl; and

$n$  is 1-3; or

$R_2$  is phenoxy optionally mono- or, independently, di-substituted with lower alkyl, lower alkoxy or halogen; and

$n$  is 2 or 3;

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- d)  $(R_3)_2CH(CH_2)_2-$ , wherein each  $R_3$ , independently, is phenyl optionally mono- or, independently, di-substituted with lower alkyl, lower alkoxy or halogen;
- e)  $R_4(CH_2)_p-$ ,  
wherein  
 $R_4$  is 2-oxopyrrolidinyl or  $(C_{2-4})$ alkoxy; and  
 $p$  is 2-4;
- f) isopropyl optionally mono-substituted in 1-position with  $(C_{1-3})$ hydroxyalkyl;
- g)  $R_5$ , wherein  $R_5$  is indanyl, a pyrrolidinyl or piperidinyl moiety optionally substituted with benzyl, a [2.2.1]- or [3.1.1]bicyclic carbocyclic moiety optionally mono- or pluri-substituted with  $(C_{1-8})$ alkyl, adamantyl or  $(C_{1-8})$ alkyl optionally mono- or, independently, pluri-substituted with hydroxy, hydroxymethyl or phenyl optionally mono- or, independently, di-substituted with lower alkyl, lower alkoxy or halogen;
- h) a substituted adamantyl  
in free form or in acid addition salt form;

in combination with at least one further  $PPAR\alpha$  compound in free or pharmaceutically acceptable salt form, for the manufacture of a medicament for the treatment a condition mediated by DPP-IV or  $PPAR\alpha$ .

14. Use of a DPP-IV inhibitor selected from

(S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine; and

(S)-1-{2-[5-cyanopyridin-2-yl]amino}ethyl-aminoacetyl-2-cyano-pyrrolidine,

in free or pharmaceutically acceptable salt form in combination with at least one further  $PPAR\alpha$  compound selected from the group consisting of fenofibrate, micronized fenofibrate, bezafibrate, gemfibrozil and ciprofibrate, or the pharmaceutically acceptable salt of such a compound for the manufacture of a medicament for the treatment a condition mediated by DPP-IV or  $PPAR\alpha$ .

15. Use of a pharmaceutical composition according to any one of claims 2 to 8 for the manufacture of a medicament for the treatment a condition mediated by DPP-IV or  $PPAR\alpha$ .

16. Use according to any one of claims 13 to 15, wherein the condition mediated by DPP-IV or  $PPAR\alpha$ , is selected from diabetes, type 2 diabetes mellitus, conditions of IGT,

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conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, obesity, dyslipidemia and osteoporosis

17. Use according to any one of claims 13 to 15, wherein the condition mediated by DPP-IV or PPAR $\alpha$ , is selected from type 2 diabetes, impaired glucose tolerance, obesity and dyslipidemia.

18. A commercial package comprising as active agents a combination of a DPP-IV inhibitor and a PPAR $\alpha$  compound together with instructions for simultaneous, separate or sequential use thereof in the prevention, delay of progression or treatment of a condition mediated by DPP-IV or PPAR $\alpha$ .

19. A kit of parts comprising

(a) an amount of a DPP IV inhibitor as defined in claim 1 or a pharmaceutically acceptable salt thereof in a first unit dosage form;

(b) an amount of at least one PPAR $\alpha$  compound or the pharmaceutically acceptable salt thereof ,

in the form of two or three or more separate units of the components (a) and (b).

20. A kit of parts according to claim 19 or a commercial package according to claim 18, wherein the DPP-IV inhibitor is selected from

(S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine; and

(S)-1-{2-[5-cyanopyridin-2-yl)amino]ethyl-aminoacetyl}-2-cyano-pyrrolidine,

and the further PPAR $\alpha$  compound is selected from the group consisting of fenofibrate, micronized fenofibrate, bezafibrate, gemfibrazil and ciprofibrate